Novel Pathways to Erythropoiesis Induced by Dimerization of Intracellular cMpl in Human Hematopoietic Progenitors.

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Public Summary:
Our research focuses on novel approaches to blood progenitor/stem cell transplantation. Transplantation is the only available curative treatment for certain blood disorders and aggressive leukemias. However, patients requiring blood progenitor/stem cell transplantation need a suitably matched bone marrow donor. Also, it takes weeks to months for blood cells to recover in patients after transplantation, leaving them vulnerable to complications such as infections and bleeding during this time. Cord blood is a more readily available source of blood progenitor/stem cells, than bone marrow donors. But its use is mainly limited to younger children because it contains a very low dose of cells that is not sufficient for older patients. A method to expand the number of cells would make it possible to use cord blood as the source of blood progenitor/stem cells for older patients, and hasten the recovery of blood cells after transplantation, thus reducing complications. We studied the use of a genetically modified form of the growth factor receptor c-Mpl for the controlled expansion of cells in cord blood. Our laboratory studies show that this strategy expands blood progenitor cells and induces the production of red blood cells by increasing cell growth, survival, and activation of red cell genes, making it a potential strategy for expediting blood cell recovery after transplantation.

Scientific Abstract:
The cytokine thrombopoietin (Tpo) plays a critical role in hematopoiesis by binding to the extracellular domain, and inducing homodimerization of the intracellular signaling domain of its receptor, cMpl. Mpl homodimerization can also be accomplished by binding of a synthetic ligand to a constitutively expressed fusion protein F36VMpl consisting of a ligand binding domain (F36V) and the intracellular signaling domain of Mpl. Unexpectedly, in contrast to Tpo stimulation, robust erythropoiesis is induced after dimerization of F36VMpl in human CD34+ progenitor cells. The goal of this study was to define the hematopoietic progenitor stages at which dimerization of intracellular Mpl induces erythropoiesis, and the downstream molecular events that mediate this unanticipated effect. Dimerization (in the absence of erythropoietin and other cytokines) in human Common Myeloid Progenitors (CMP) and Megakaryocytic-Erythroid Progenitors (MEP) caused a significant increase in CD34+ cells ($p<0.01$) and induced all stages of erythropoiesis including production of enucleated red blood cells. In contrast, erythropoiesis was not seen with Tpo stimulation. CD34+ cell expansion was the result of increased cell cycling and survival ($p<0.05$). Microarray profiling of CD34+ cells demonstrated that a unique transcriptional pattern is activated in progenitors by F36VMpl dimerization. Ligand-inducible dimerization of intracellular Mpl in human myelo-erythroid progenitors induces progenitor expansion and erythropoiesis through molecular mechanisms that are not shared by Tpo stimulation of endogenous Mpl.